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10/596,132	06/01/2006	Cristiano Chiamulera	PB60599USW	2666

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GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY, MAI B482
FIVE MOORE DR., PO BOX 13398
RESEARCH TRIANGLE PARK, NC 27709-3398

EXAMINER	
BLAKELY III, NELSON CLARENCE	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
10/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USCIPRTP@GSK.COM
LAURA.M.MCCULLEN@GSK.COM
JULIE.D.MCFALLS@GSK.COM

Office Action Summary	Application No.	Applicant(s)	
	10/596,132	CHIAMULERA ET AL.	
	Examiner	Art Unit	
	NELSON C. BLAKELY III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 6* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/01/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 5 and 6 of the instant application are pending. Claims 1-4 were canceled pursuant to Applicant's Amendment filed 06/01/2006. Thus, instant claims 5 and 6 are presented for examination on their merits.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on 12/02/2003. It is noted, however, that applicant has not filed a certified copy of the GB Serial No. 0327912.2 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

The information disclosure statement filed 06/01/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein, indicated where lined through, has not been considered.

Objections

Specification

The disclosure is objected to because of the following informalities:

The spacing of the lines of the specification is such as to make reading difficult. New application papers with lines 1½ or double spaced on good quality paper are required.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claims

Claim 6 is objected to because of the following informalities:

With regard to instant claim 6, it appears that the recitation meglumine is misspelled as meglu**a**mine in line 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite the limitation "solvate" in reference to the instantly claimed compound of Formula (I). Applicant has not described the claimed genus of "solvate" in a manner that would indicate that Applicant was in possession of the full scope of this genus, or even to describe what this genus is comprised of. The instant specification, page 1, lines 13 and 14 of text, for example, discloses that the compounds of general Formula (I) may be in the form of solvates, e.g. hydrates. This recitation is not a definition that allows the Examiner to ascertain that Applicant was in possession of the full scope of this genus.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP § 2163. In particular, Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere with or plan for obtaining the claimed chemical invention." Eli Lilly, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent

Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jane. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, *inter aria*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lily and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. Univ. of Rochester v. G.D. Searle & Co., 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, Applicants have not described the genus of "solvate" in a manner that would allow one skilled in the art to immediately envisage the compounds contemplated for use. As such, the claims lack adequate written description for the claimed "solvate".

Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of nicotine craving in a human, comprising administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt, does not reasonably provide enablement for a solvate. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in the MPEP § 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

It is noted that all of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The State of the Prior Art and the Predictability or lack thereof in the art

Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and

in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization (Morissette et al., Advanced Drug Delivery Reviews, Vol. 56, pages 275-300; 2004). Therefore, for these reasons, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during

various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al., Advanced Drug Delivery Reviews, Vol. 48, Abstract; 2001). In further discussing the predictability of the formation of solvates, Vippagunta et al. discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

The Amount of Direction or Guidance Present and Presence or Absence of Working Examples

The only direction or guidance present in the instant specification is for compounds of Formula (I) in instant claim 5, as well as pharmaceutically acceptable salts. There is no data present in the specification for the preparation of solvates of compounds of Formula (I). The specification only discloses on page 1, lines 13 and 14 of text, for example, discloses that the compounds of general Formula (I) may be in the form of solvates, e.g. hydrates. The guidance in the specification is limited to the disclosure that certain compounds can exist in solvate form; however, it is not discussed which specific compounds can exist in these forms. Finally, there are no working examples present in the disclosure that specifically indicate the preparation of solvates. In each of the working examples, the compound is placed in solution, but finally the

solvent was removed to give a solid, resulting in the original compound, not a solvated form.

The Breadth of the Claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any solvate of the claimed compounds.

The Quantity of Experimentation Needed and the Level of Skill in the Art

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare *any* solvate of the compounds of Formula (I). The science of crystallization has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being obvious over Di Fabio (International Publication No. WO99/64411A1), as evidenced by Berge *et al* (Journal of Pharmaceutical Sciences, Vol. 66, No. 1, pages 1-19; 1977).

With regard to instant claims 5 and 6, Di Fabio discloses in reference claims 1-6, 8 and 19 a method of treatment of a mammal including man for conditions where antagonizing the effects of excitatory amino acids on the NMDA receptor complex is of therapeutic benefit comprising administration of an effective amount of a compound (as claimed in any of claims 1 to 16), wherein the compound is a compound of Formula (I), wherein **X** may be a carbon atom, **R** may be a chlorine atom, $\mathbf{R_1}$ may be a hydrogen atom, **A** may be $-CH_2-$, **Y** may be methylene, and $\mathbf{R_2}$ may be a phenyl group, or physiologically acceptable salts, for example. Taking the aforementioned substituents of the instant reference into consideration would result in a substantially similar, if not identical, instantly claimed compound of Formula **(I)**. Additionally, Di Fabio discloses on page 4, lines 20-27 of the instant reference that suitable physiologically acceptable

salts of the compounds of the referenced invention include base addition salts and, where appropriate, acid addition salts. Di Fabio also discloses on page 10, line 16 through page 11, line 4 and page 11, lines 26-31 of the instant reference specification that the compounds of the referenced invention are potent antagonists of the NMDA receptor complex, thus, useful in the treatment of withdrawal symptoms from nicotine (e.g. smoking cessation) benzodiazepines, for example.

Di Fabio fails to disclose wherein the pharmaceutically, or physiologically, acceptable salt is meglumine; however, Berge *et al* recite in Table I FDA-approved commercially marketed salts used in pharmaceutical formulations. In the instant excerpt, 2.29% of anionic or cationic salts used through 1974 were that of meglumine.

Therefore, a skilled artisan would envisage the use of meglumine as a suitable pharmaceutical, or physiologically, acceptable salt as evidenced by Berge *et al* with the compound of Formula (I) as taught by Di Fabio. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references to yield a more bioavailable product for administration to patients prepared in a form suitable for ease of isolation in a large scale manufacture. It would have been obvious to one of ordinary skill in the art at the time of the invention because the combined teachings of the prior art is fairly suggestive of the claimed invention.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in

the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being obvious over Orlandi (International Publication No. WO01/42238A1).

With regard to instant claims 5 and 6, Orlandi discloses in reference claims 1 and 8 a method of treatment of a mammal including man for conditions where antagonizing the effects of excitatory amino acids on the NMDA receptor complex is of therapeutic benefit, comprising administration of an effective amount of a compound (as claimed in any of claims 1 to 3), wherein the compound may be the meglumine salt of enantiomer A of 7-chloro-4-(2-oxo-1-phenyl-3-pyrrolidinylidene)-1,2,3,4-tetrahydro-2-quinolinecarboxylic acid [the instantly claimed compound of Formula (I)]. Additionally, Orlandi discloses on page 3, line 13 through page 4, line 9 and page 4, line 32 through page 5, line2 of the instant reference specification that the compounds of the referenced

invention are potent antagonists of the NMDA receptor complex, thus, useful in the treatment of withdrawal symptoms from nicotine (e.g. smoking cessation) benzodiazepines, for example.

Therefore, a skilled artisan would envisage the use of the meglumine salt of the compound of Formula (I) as disclosed by Orlandi in the treatment of withdrawal symptoms from nicotine following smoking cessation referenced by Orlandi. One of ordinary skill in the art would have been motivated to combine the teachings of the aforementioned references to yield a readily prepared and isolated relatively pure form of the compound of Formula (I) for use on a large scale. A skilled artisan also would have been motivated to combine the disclosure of Orlandi to yield a preparation with a high degree of purity and good stability, thus fulfilling the exacting criteria required for pharmaceutical compositions for administration to patients. It would have been obvious to one of ordinary skill in the art at the time of the invention because the combined teachings of the prior art is fairly suggestive of the claimed invention.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR

1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NELSON C. BLAKELY III whose telephone number is (571) 270-3290. The examiner can normally be reached on Mon - Thurs, 7:00 am - 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/N. C. B. III/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614